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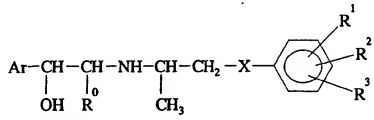
(54) Title: USE OF PHENETHANOLAMINE DERIVATIVES IN THE TREATMENT OF GASTROINTESTINAL DISORDERS

(57) Abstract

The use of compounds of formula (I) in which: R^0 is hydrogen, methyl or hydroxymethyl; R^1 is substituted alkyl; R^2 and R^3 are each hydrogen, halogen, hydroxy, alkoxy, carboxy, alkoxycarbonyl, alkyl, nitro, haloalkyl group, or substituted alkyl; X is oxygen or sulphur; and Ar is optionally substituted phenyl or naphtyl; and pharmaceutically acceptable salts thereof in the treatment of gastrointestinal disorders is described.



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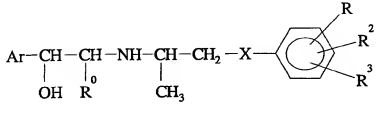
USE OF PHENETHANOLAMINE DERIVATIVES IN THE TREATMENT OF GASTROINTESTINAL DISORDERS

This invention relates to a new medical use for certain phenethanolamine derivatives and to pharmaceutical compositions containing them. In particular, the invention relates to the use of such compounds which act as agonists at atypical beta-adrenoceptors (also known as beta-3-adrenoceptors). Such receptors have been described for example by J R S Arch *et. al., Nature*, 309, 163-165 (1984); C Wilson *et. al., Eur. J. Pharmacol.*, 100, 309-319 (1984); L J Emorine *et. al., Science*, 245, 1118-1121 (1989); and A. Bianchetti *et. al. Br. J. Pharmacol.*, 100, 831-839 (1990).

Atypical beta-adrenoceptors belong to the family of adrenoceptors which mediate the physiological actions of the hormones adrenaline and noradrenaline. Sub-types of the adrenoceptors, α_1-, α_2-, β_1-, β_2- and β_3-(atypical) can be identified on the basis of their pharmacological properties and physiological effects. Chemical agents which stimulate or block these receptors (but not β_3) are widely used in clinical medicine. More recently, emphasis has been placed upon specific receptor selectivity in order to reduce side effects caused, in part, by interactions with other receptors.

Atypical beta-adrenoceptors are known to occur in adipose tissue and the gastrointestinal tract. Compounds which act as agonists at atypical beta-adrenoceptors may be identified using standard tests (see for instance C Wilson *et. al., supra*).

A particular class of phenethanolamine compounds have been described in European Patent Specification No. 0 543 662-A which describes compounds of the general formula (I)



(I)

wherein

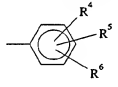
R^0 is a hydrogen atom, a methyl group or a hydroxymethyl group;

R^1 is a substituted C_{1-12}alkyl group which group is substituted by at least one of the substituents A, defined below;

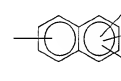
R^2 and R^3 are each selected from a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-5}alkoxy group, a carboxy group, a C_{2-7}alkoxycarbonyl group, a C_{1-5}alkyl group, a nitro group, a haloC_{1-4}alkyl group, or a substituted C_{1-12}alkyl group which group is substituted by at least one of substituents A, defined below;

X is an oxygen atom or a sulphur atom; and

Ar is a group of formula (C) or (D):



(C)



(D)

in which:

R^4 is a hydrogen atom, a halogen atom, a hydroxy group, a hydroxymethyl group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, an aliphatic carboxylic C_{1-6}acyloxy group, a nitro group, a cyano group, an aralkyloxy group in which the aralkyl part is as defined below, an aryloxy group in which the aryl part is as defined below, an aryl group as defined below, or a haloC_{1-4}alkyl group;

R^5 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, or a nitro group;

R^6 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, or a C_{1-5}alkyl group;

said aralkyl part is a C_{1-3}alkyl group which group is substituted by 1 or 2 aryl groups as defined below;

said aryl groups are carbocyclic C_{6-10}aryl groups which are unsubstituted or are substituted by at least one of substituents B, defined below;

said substituents A are selected from carboxy groups, C_{2-7}alkoxycarbonyl groups, aryloxycarbonyl groups in which the aryl part is as defined above, aralkyloxycarbonyl groups in which the aralkyl part is as defined above, C_{1-6} alkylcarbamoyl groups, dialkylcarbamoyl groups in which each alkyl part has from 1 to 4 carbon atoms, carbamoyl groups, hydroxycarbamoyl groups, hydroxy groups, carboxylic acyloxy groups having from 1 to 6 carbon atoms, and 2,4-dioxothiazolidin-5-yl groups; and

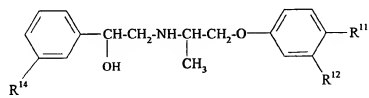
said substituents B are selected from halogen atoms, C_{1-4}alkyl groups, C_{1-3}alkoxy groups, nitro groups, haloC_{1-4}alkyl groups, and hydroxy groups; and pharmaceutically acceptable salts thereof.

These compounds are described as being of use in the treatment or prophylaxis of diabetes, obesity, hyperlipemia, hyperglycaemia, complications of diabetes, obesity related hypertension and osteoporosis.

In general, atypical beta-adrenoceptor agonists have been found to be particularly useful as thermogenic anti-obesity agents and as anti-diabetic agents. Compounds having atypical beta-adrenoceptor agonist activity have also been described as being useful in the treatment of hyperglycaemia, as animal growth promoters, as blood platelet aggregation inhibitors, as positive inotropic agents and as antiathereosclerotic agents, and as being useful in the treatment of glaucoma.

It has now been found that the compounds of general formula (I) which act as agonists at atypical beta-adrenoceptors may be useful for the treatment of gastrointestinal disorders, especially inflammatory gastrointestinal disorders including peptic ulceration, oesophagitis, gastritis and duodenitis (including that induced by H.pylori), intestinal ulcerations (including inflammatory bowel disease, especially, ulcerative colitis, ileitis, Crohn's disease and proctitis) and gastrointestinal ulcerations, especially when induced by non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

A preferred sub-class of the compounds of the general formula (I) for use according to the present invention is that defined by formula (II)



(II)

and physiologically acceptable salts and solvates thereof, wherein

one of R^{11} and R^{12} represents a hydrogen atom and the other of R^{11} and R^{12} represents the group $-CH_2CO_2H$; and
R^{14} represents a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group.

It will be appreciated that the above compounds of formulae (I) and (II) are optically active. The use of both the individual, isolated isomers and mixtures thereof, including racemates, is also considered to be within the scope of the present invention. Particularly preferred compounds of formulae (I) and (II) for use according to the present invention are those wherein the asymmetric carbon atoms in the -CH(OH)- group and the $-CH(CH_3)-$ group are in the (R)-configuration.

Another preferred group of compounds of formula (II) is that wherein R^{11} represents the group $-CH_2CO_2H$.

A particularly preferred compound of general formula (I) for use according to the present invention is:
(R,R)-[4-[2-[2-[(3-chlorophenyl)-2-hydroxy-ethylamino]propoxy]phenyl]acetic acid;
or a physiologically acceptable salt or solvate thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, citrates, oxalates, maleates, salicylates, fumarates, succinates, lactates, glutarates, glutaconates, acetates or tricarballyates. The compounds may also form salts with suitable bases. Examples of such salts include alkali metal (e.g. sodium or potassium), alkaline earth metal (e.g. calcium, or magnesium), ammonium and substituted ammonium.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable, but other salts may find use, for example, in

the preparation of the compounds of general formula (I) and the physiologically acceptable salts thereof.

The present invention provides a method of treatment of a human or non-human mammal, suffering from or susceptible to a inflammatory gastrointestinal disorder, such as peptic ulceration, oesophagitis, gastritis, duodenitis, intestinal ulcerations and gastrointestinal ulcerations, which method comprises administering to said mammal an effective amount of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

In a preferred aspect of the present invention, there is provided a method of treatment of a human or non-human mammal, suffering from a condition of intestinal ulcerations wherein said condition is an inflammatory bowel disease, such as ulcerative colitis, ileitis, Crohn's disease or proctitis, which method comprises administering to said mammal an effective amount of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

In a particularly preferred aspect of the present invention, there is provided a method of treatment of a human or non-human mammal, suffering from a condition of gastrointestinal ulcerations wherein said condition is induced by non-steroidal anti-inflammatory drugs, which method comprises administering to said mammal an effective amount of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

References in this specification to treatment include prophylactic treatment as well as the alleviation of symptoms.

In a further aspect, the present invention provides a therapeutic agent which comprises an effective amount of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in medicine, particularly human medicine, for the treatment of inflammatory gastrointestinal disorders such as peptic ulceration, oesophagitis, gastritis, duodenitis, intestinal ulcerations and gastrointestinal ulcerations.

In a further preferred aspect of the present invention, there is provided a therapeutic agent which comprises an effective amount of a compound of

general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of a condition of intestinal ulcerations wherein said condition is an inflammatory bowel disease such as ulcerative colitis, ileitis, Crohn's disease or proctitis.

In a further particularly preferred aspect of the present invention, there is provided a therapeutic agent which comprises an effective amount of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of a condition of gastrointestinal ulcerations wherein said condition is induced by non-steroidal anti-inflammatory drugs.

In a yet further aspect, the invention provides for the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of inflammatory gastrointestinal disorders such as peptic ulceration, gastritis, duodenitis, intestinal ulcerations and gastrointestinal ulcerations.

In a yet further preferred aspect of the present invention, there is provided the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a condition of intestinal ulcerations wherein said condition is an inflammatory bowel disease such as ulcerative colitis, ileitis, Crohn's disease or proctitis.

In a yet further particularly preferred aspect of the present invention, there is provided the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of a condition of gastrointestinal ulcerations wherein said condition is induced by non-steroidal anti-inflammatory drugs.

It will be appreciated that where a compound of general formula (I) or a physiologically acceptable salt or solvate thereof is used for the treatment of a condition of gastrointestinal ulcerations induced by non-steroidal anti-inflammatory drugs (NSAID's) it may be preferable to co-adminster the compound of general formula (I) together with the NSAID. The active ingredients may be employed in the form of separate pharmaceutical formulations or a combined formulation may be used. In such a combined

formulation, the active ingredients must of course be stable and mutually compatible in the particular formulation employed.

Pharmaceutical compositions which comprise at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof and at least one non-steroidal anti-inflammatory drug, together with at least one physiologically acceptable carrier or excipient are believed to be novel compositions and constitute a further aspect of the present invention.

It will be appreciated that similar combined formulations may be utilised for the treatment of a condition of gastrointestinal ulcerations induced by corticosteroids.

The compound of general formula (I) and their physiologically acceptable salts and solvates may be formulated for administration in any convenient way, and the present invention also includes within its scope pharmaceutical compositions comprising at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof adapted for use in human or veterinary medicine. Such compositions may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients. The carrier(s) or excipient(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus the compounds for use according to the present invention may be formulated for oral, buccal, parenteral, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents

(e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for use according to the present invention may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds for use according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or

intramuscularly) or by intramuscular injection. Thus, for example, the compounds for use according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A proposed dose of the compounds for use according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, preferably to 1mg to 100mg of the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of general formula (I) for use according to the present invention may be prepared by a number of processes which are well known in the art for the preparation of phenethanolamine derivatives. Suitable methods are described, for instance, in European Patent Specification No. 0 543 662-A.

The following, non-limiting, examples illustrate the synthesis of compounds of general formula (I) for use according to the present invention.

Temperatures are in °C. Thin layer chromatography (T.l.c.) was carried out over SiO_2 unless otherwise specified, and "dried" refers to drying using magnesium sulphate except where otherwise stated.

Intermediate 1

Methane sulfonic acid, (R)-(2-benzyloxycarbonylamino)-propyl ester

To a stirred solution of (R)-1-(2-hydroxy-1-methylethyl)carbamic acid, benzyl ester (14.95g) in dichloromethane (200ml) maintained at -10° was added triethylamine (7.9g) followed by methanesulphonyl chloride (8.93g), which was added dropwise, maintaining the temperature of the reaction at -10°. The reaction was stirred at this temperature for 1.5h, then concentrated under reduced pressure. The residue was partitioned between water and ethyl

acetate, and the aqueous phase was extracted further with ethyl acetate. The combined organic extracts were washed successively with N hydrochloric acid, aqueous sodium bicarbonate solution, and saturated brine, dried and evaporated to give the title compound as a colourless solid (18.81g), which was used without purification.

n.m.r. ($CDCl_3$): δ 1.27(d, 3H), 2.99 (s, 3H), 4.07 (m, 1H), 4.16 (m, 1H) and 4.27 (m, 1H), 4.86 (br.s, 1H), 5.11 (s, 2H), 7.3-7.4 (m, 5H).

Intermediate 2

(R)-2-[4-[(2-Benzyloxycarbonylamino)propoxy]phenyl]acetamide

Sodium hydride (60% dispersion in oil, 2.86g) was added cautiously to a stirred solution of 4-hydroxyphenylacetamide (10.4g) in dry N,N-dimethylformamide (150ml) under an atmosphere of nitrogen. The mixture was stirred for 3h, a solution of Intermediate 1 (18.77g) was added and the mixture was heated at 60° for 3.5h, then allowed to stand at ambient temperature for 72h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was separated, washed with water, dried, and evaporated. A portion of this residue (10g) was chromatographed on silica, eluting with 10% methanol in chloroform. Concentration of the appropriate fractions gave the title compound as a cream-coloured solid (2.71g, contains an impurity).

n.m.r. (DMSO-d_6): δ 1.14 (d, 3H), 3.32 (s, 2H), 3.48 (m, 1H), 3.75-3.95 (m, 2H), 5.01 (s, 2H), 6.80-6.88 (m, 2H), 7.12-7.18 (m, 2H), 7.28-7.45 (m, 5H).

Intermediate 3

(R)-2-[4-(2-Amino-1-propoxy)phenyl]acetamide

A suspension of Intermediate 2 (2.7g), 10% palladium on charcoal (280 mg) and dry ammonium formate (1.67g) in methanol (230 ml) was stirred and heated under reflux under an atmosphere of nitrogen for 4h. The catalyst was filtered off, and the filtrate was concentrated. The residue was chromatographed on silica, eluting with chloroform:methanol:0.880 ammonium hydroxide (60:10:1). Evaporation of the appropriate fractions gave the title compound (contaminated with 4-hydroxyphenylacetamide) as a colourless solid (1.51g).

n.m.r. (DMSO-d_6 + D_2O): δ 1.05 (d, 3H), 3.12 (m, 1H), 3.28 (s, 1H), 3.66-3.74 (m, 2H), 6.86 (d, 2H), 7.15 (d, 2H).

Intermediate 4

(R,R)-2-[4-[2-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]propoxy]-phenyl] acetamide

A solution of Intermediate 3 (1.4g) and trimethylsilylacetamide (0.95g) in dimethylsulphoxide (5ml) were stirred under an atmosphere of nitrogen for 2h, then (R)-3-chlorophenyloxirane (1.03g) was added, and the solution was maintained at 70° for 6 days. The solution was poured into a mixture of 2N hydrochloric acid and ethyl acetate; the phases were separated, and the aqueous phase was washed with more ethyl acetate. The aqueous phase was basified and extracted with ethyl acetate. The combined organic extracts were dried and evaporated, and the residue was chromatographed on silica, eluting with 10% methanol in chloroform. Concentration of the appropriate fractions gave the title compound as a colourless solid (0.645mg), m.p. 122-125°

$[\alpha^D]$ -16.1° (c 0.4 MeOH).

Assay Found: C 62.8; H 6.5; N 7.85%

$C_{19}H_{23}ClN_2O_3$ requires: C 62.9; H 6.4; N 7.85%

Example 1

(R,R)-[4-[2-[2-(3-Chlorophenyl)-2-hydroxy-ethylamino]propoxy]phenyl]acetic acid

Intermediate 4 (490mg) in 2N hydrochloric acid (14ml) was heated under reflux for 70 min. The mixture was cooled and evaporated. The residue was dissolved in water, the solution was filtered, and the filtrate freeze-dried to give a cream-coloured solid (504mg). A solution of this solid in water was chromatographed on Amberlite XAD-2, eluting with aqueous ethanol. The appropriate fractions were combined, concentrated, and freeze-dried to give the title compound (147mg) as a colourless solid.

Assay Found: C 60.1; H 6.0; N 3.95%

$C_{19}H_{22}ClNO_4.H_2O$ requires: C 59.8; H 6.3; N 3.7%

n.m.r. (DMSO-d_6): δ 1.10 (d, 3H), 2.81 (m, 2H), 3.12 (m, 1H), 3.50 (s, 2H), 3.85 (m, 2H), 4.69 (m, 1H), 6.87 (d, 2H) 7.16 (d, 2H), 7.27-7.44 (m, 4H).

Atypical beta-adrenoceptor agonists are compounds which demonstrate a pharmacological response (*in vitro* or *in vivo*) mediated at atypical beta-adrenoceptors. This activity has been be measured as the ability to

stimulate lipolysis by rat adipocytes at sub-micromolar concentrations, in a response that is resistant to blockade by standard beta-adrenoceptor blocking drugs such as propranolol.

Another useful means of identifying an atypical beta-adrenoceptor agonist involves the measurement of agonist activity at atypical beta-adrenoceptors in the rat isolated lower oesophagus. A suitable assay is described below as Method 1. Typically in this assay, a compound of general formula (I) for use according to the present invention has an equipotent molar ratio (EPMR) relevant to isoprenaline of less than 30.

The rat oesophagus assay is based upon that described by Ford *et. al.*, *Br. J. Pharmacol.*, 105(suppl.), 235P, 1992, the method of which is described below as Method 1:

Method 1

The lower oesophagus is removed from male AH/A rats (100-150g). The overlying serosal muscle is removed from the oesophagus to leave the tunis muscularis mucosa. Tissues are then placed in Kreb's solution containing the β_2-antagonist ICI 118,551 (10^{-6}M), the β_1-antagonist atenolol (10^{-5}M), the phosphodiesterase inhibitor isobutyl methyl xanthine (IBMX; $3x10^{-6}$M) and the prostaglandin synthesis inhibitor indomethacin ($3x10^{-6}$M), and the tissues suspended under a resting tension of 0.5g.

Subsequently, tissues are contracted with a submaximal concentration of carbachol (10^{-6}M) and, when a stable increase in tension has been achieved, a cumulative concentration effect curve to isoprenaline is constructed. Following washout with fresh Kreb's solution, tissues are recontracted with carbachol (10^{-6}M) and a cumulative concentration effect curve to test agonist is constructed.

The relative potency of each test agonist (EPMR) is compared to isoprenaline as follows:

$$EPMR = \frac{EC_{50} \text{ agonist}}{EC_{50} \text{ isoprenaline}}$$

wherein EC_{50} is the molar concentration of agonist which produces 50% of the maximum possible response for that agonist.

Using the non-selective beta-adrenoceptor agonist isoprenaline as a reference agonist, compounds selective for atypical beta-adrenoceptors should preferably be a minimum of 10-30 times less potent than isoprenaline at $ß_1$- or $ß_2$-adrenoceptors and, more preferably, 300-1000 times less potent than isoprenaline at $ß_1$- or $ß_2$-adrenoceptors.

An experimental model in which atypical beta-adrenoceptor agonists may be shown to be of use in the treatment of gastrointestinal disorders is described below as Method 2. The procedure is based upon that described by H. Satoh *et al.*, *Gastroenterology*, 81, 719-725 (1981) in which the effect of compounds on indomethacin-induced gastric antral lesions in the re-fed rat is investigated. Indomethacin is an example of the class of compound known as non-steroidal anti-inflammatory drugs (NSAIDs), the use of which is frequently associated with gastrointestinal ulcers.

Method 2

Food (but not water) is withheld from female random hooded rats (70-120g) for 24 hours and then the rats are re-fed with Rat and Mouse No. 1 Maintenance Diet. After 1 hour of access to food, the rats are dosed orally with either the test compound or solvent (0.5% w/v methyl cellulose in water). 30 minutes later, indomethacin (60mg/kg; dissolved in 1% w/v $NaHCO_3$ in saline) is administered as a single subcutaneous injection at the back of the neck. Subsequently, the rats are allowed food, but water is withheld, and the animals are humanely killed by cervical dislocation at 6 hours post dose. Control animals received a single subcutaneous dose of the appropriate solvent.

The rat's stomach is removed (with a small amount of duodenum attached), opened along the greater curvature and the contents removed by washing with

0.9% w/v sodium chloride solution (saline). The opened stomach is pinned out (mucosal surface uppermost) on a polystyrene mat and the area of damage assessed by placing a grid (composed of 1mm squares) over the antral region. Antral damage appears as discrete black or dark brown ulcers. The total area of antral damage is then expressed as a percentage of the total surface area of the antrum.

The protective effect of the test compound on indomethacin-induced antral damage is calculated as a percentage using the following equation:

$$100 \times \frac{\text{\% area of damage with NSAID} - \text{\% area of damage with NSAID + test compound}}{\text{\% area of damage with NSAID}}$$

Results

The gastro-protective effects of (R,R)-[4-[2-[2-(3-chlorophenyl)-2-hydroxy-ethylamino]propoxy]phenyl]acetic acid (Example 1) administered as a single intravenous (i.v.) dose or oral (p.o.) dose 30 minutes before indomethacin, is shown by the following data:

i.v. administration			**p.o. administration**		
ED_{50} (mg/kg)	dose (mg/kg)	protection (%)	ED_{50} (mg/kg)	dose (mg/kg)	protection (%)
0.12	1.0	90	1.0	1.0	57

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression Tablet

	mg/tablet
(i) Active Ingredient	4.688
Calcium Hydrogen Phosphate BP*	83.06
Croscarmellose Sodium NF	1.8
Magnesium Stearate BP	0.45
Compression weight	90.0

* of a grade suitable for direct compression.

The active ingredient is passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 5.5mm, flat bevelled edge punches.

	mg/tablet
(ii)Active Ingredient.	0.31
Anhydrous Lactose USNF	131.99
Pregelatinised Starch USNF	7.0
Magnesium Stearate BP	0.7
Compression weight	140.0

The active ingredient is passed through a 60 mesh sieve, and blended with the lactose, pregelatinised starch and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 7.5mm normal concave punches.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup		mg/5ml dose
Active Ingredient		2.5
Sucrose BP		2750.0
Glycerine BP		500.0
Buffer)		
Flavour)		
Colour)		as required
Preservative)		
Purified Water BP	to	5.0ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup is clarified by filtration.

B. Sucrose-free Syrup		mg/5ml dose
Active Ingredient		2.5
Hydroxypropylmethylcellulose USP (viscosity type 4000)		22.5
Buffer)		
Flavour)		
Colour)	as required	
Preservative)		
Sweetener)		
Purified Water BP	to	5.0ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION FOR INTRAVENOUS ADMINISTRATION

	µg/ml
(i) Active Ingredient	800
Dilute Hydrochloric Acid BP to pH 3.5	
Sodium Chloride Injection BP to 1ml	

The active ingredient is dissolved in a suitable volume of Sodium Chloride Injection BP, the pH of the resultant solution is adjusted to pH3.5 with dilute hydrochloric acid BP then the solution is made to volume with sodium chloride injection BP and thoroughly mixed. The solution is filled into Type I clear glass 5ml ampoules which are sealed under a headspace of air, by fusion of the glass then sterilised by autoclaving at 120^0 for not less than 15 minutes.

	µg/ml
(ii) Active ingredient	56.2
Sodium Chloride BP	as required
Water for Injection BP to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively, the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

SUPPOSITORY FOR RECTAL ADMINISTRATION

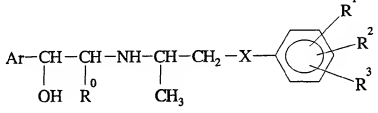
Active ingredient		49.0 mg
Witepsol* H15	to	1.0g

*a proprietary grade of Adeps Solidus Ph.Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled using suitable machinery, into 1g size suppository moulds.

CLAIMS

1. A method of treatment of a human or non-human mammal suffering from or susceptible to an inflammatory gastrointestinal disorder which method comprises administering to said mammal an effective amount of compound of formula (I):



(I)

wherein

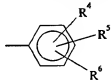
R^0 is a hydrogen atom, a methyl group or a hydroxymethyl group;

R^1 is a substituted C_{1-12}alkyl group which group is substituted by at least one of the substituents A, defined below;

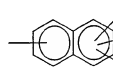
R^2 and R^3 are each selected from a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-5}alkoxy group, a carboxy group, a C_{2-7}alkoxycarbonyl group, a C_{1-5}alkyl group, a nitro group, a haloC_{1-4}alkyl group, or a substituted C_{1-12}alkyl group which group is substituted by at least one of substituents A, defined below;

X is an oxygen atom or a sulphur atom; and

Ar is a group of formula (C) or (D):



(C)



(D)

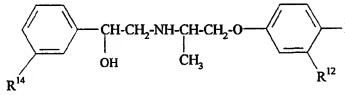
in which:

R^4 is a hydrogen atom, a halogen atom, a hydroxy group, a hydroxymethyl group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, an aliphatic carboxylic C_{1-6}acyloxy group, a nitro group, a cyano group, an aralkyloxy group in which the aralkyl part is as defined below, an aryloxy group in which the aryl part is as defined below, an aryl group as defined below, or a haloC_{1-4}alkyl group;

R^5 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, or a nitro group;

R^6 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, or a C_{1-5}alkyl group;
said aralkyl part is a C_{1-3}alkyl group which group is substituted by 1 or 2 aryl groups as defined below;
said aryl groups are carbocyclic C_{6-10}aryl groups which are unsubstituted or are substituted by at least one of substituents B, defined below;
said substituents A are selected from carboxy groups, C_{2-7}alkoxycarbonyl groups, aryloxycarbonyl groups in which the aryl part is as defined above, aralkyloxycarbonyl groups in which the aralkyl part is as defined above, C_{1-6} alkylcarbamoyl groups, dialkylcarbamoyl groups in which each alkyl part has from 1 to 4 carbon atoms, carbamoyl groups, hydroxycarbamoyl groups, hydroxy groups, carboxylic acyloxy groups having from 1 to 6 carbon atoms, and 2,4-dioxothiazolidin-5-yl groups; and
said substituents B are selected from halogen atoms, C_{1-4}alkyl groups, C_{1-3}alkoxy groups, nitro groups, haloC_{1-4}alkyl groups, and hydroxy groups;
and pharmaceutically acceptable salts thereof.
or a physiologically acceptable salt or solvate thereof.

2. A method as claimed in Claim 1 wherein the compound of formula (I), or physiologically acceptable salt or solvate thereof, is selected from compounds of formula (II)



(II)

and physiologically acceptable salts and solvates thereof,
wherein
one of R^{11} and R^{12} represents a hydrogen atom and the other of R^{11} and R^{12} represents the group $-CH_2CO_2H$; and
R^{14} represents a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group.

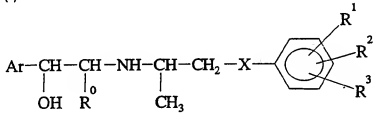
3. A method as claimed in Claim 2 wherein R^{11} is $-CH_2CO_2H$.

4. A method as claimed in any one of Claims 1 to 3 wherein the compound of formula is (I) (R,R)-[4-[2-[2-[(3-chlorophenyl)-2-hydroxy-ethylamino]propoxy] phenyl]acetic acid.

5. A method as claimed in any one of Claims 1 to 4 wherein the inflammatory gastrointestinal disorder is an inflammatory bowel disease selected from ulcerative colitis, ileitis, Crohn's disease and proctitis.

6. A method as claimed in any one of Claims 1 to 4 wherein the inflammatory gastrointestinal disorder is a condition of gastrointestinal ulcerations, said condition induced by non-steroidal anti-inflammatory drugs.

7. A therapeutic agent which comprises an effective amount of a compound of formula (I):



(I)

wherein

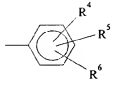
R^0 is a hydrogen atom, a methyl group or a hydroxymethyl group;

R^1 is a substituted C_{1-12}alkyl group which group is substituted by at least one of the substituents A, defined below;

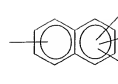
R^2 and R^3 are each selected from a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-5}alkoxy group, a carboxy group, a C_{2-7}alkoxycarbonyl group, a C_{1-5}alkyl group, a nitro group, a haloC_{1-4}alkyl group, or a substituted C_{1-12}alkyl group which group is substituted by at least one of substituents A, defined below;

X is an oxygen atom or a sulphur atom; and

Ar is a group of formula (C) or (D):



(C)



(D)

in which:

R^4 is a hydrogen atom, a halogen atom, a hydroxy group, a hydroxymethyl group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, an aliphatic carboxylic C_{1-6}acyloxy group, a nitro group, a cyano group, an aralkyloxy group in which the aralkyl part is as defined below, an aryloxy group in which the aryl part is as defined below, an aryl group as defined below, or a haloC_{1-4}alkyl group;

R^5 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, or a nitro group;

R^6 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, or a C_{1-5}alkyl group;

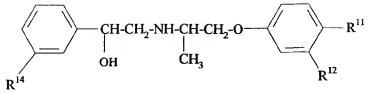
said aralkyl part is a C_{1-3}alkyl group which group is substituted by 1 or 2 aryl groups as defined below;

said aryl groups are carbocyclic C_{6-10}aryl groups which are unsubstituted or are substituted by at least one of substituents B, defined below;

said substituents A are selected from carboxy groups, C_{2-7}alkoxycarbonyl groups, aryloxycarbonyl groups in which the aryl part is as defined above, aralkyloxycarbonyl groups in which the aralkyl part is as defined above, C_{1-6} alkylcarbamoyl groups, dialkylcarbamoyl groups in which each alkyl part has from 1 to 4 carbon atoms, carbamoyl groups, hydroxycarbamoyl groups, hydroxy groups, carboxylic acyloxy groups having from 1 to 6 carbon atoms, and 2,4-dioxothiazolidin-5-yl groups; and

said substituents B are selected from halogen atoms, C_{1-4}alkyl groups, C_{1-3}alkoxy groups, nitro groups, haloC_{1-4}alkyl groups, and hydroxy groups; or a physiologically acceptable salt or solvate thereof for use in the treatment of an inflammatory gastrointestinal disorder.

8. A therapeutic agent as claimed in Claim 7 wherein the compound of formula (I), or physiologically acceptable salt or solvate thereof, is selected from compounds of formula (II):



(II)

and physiologically acceptable salts and solvates thereof,
wherein
one of R^{11} and R^{12} represents a hydrogen atom and the other of R^{11} and R^{12} represents the group $-CH_2CO_2H$; and
R^{14} represents a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group.

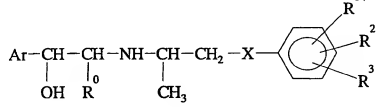
9. A therapeutic agent as claimed in Claim 8 wherein R^{11} is $-CH_2CO_2H$.

10. A therapeutic agent as claimed in any one of Claims 7 to 9 wherein the compound of formula (I) is (R,R)-[4-[2-[2-[(3-chlorophenyl)-2-hydroxyethylamino]propoxy]phenyl]acetic acid.

11. A therapeutic agent as claimed in any one of Claims 7 to 10 wherein the inflammatory gastrointestinal disorder is an inflammatory bowel disease selected from ulcerative colitis, ileitis, Crohn's disease and proctitis.

12. A therapeutic agent as claimed in any one of Claims 7 to 10 wherein the inflammatory gastrointestinal disorder is a condition of gastrointestinal ulcerations, said condition induced by non-steroidal anti-inflammatory drugs.

13. The use of a compound of formula (I):



(I)

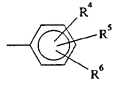
wherein
R^0 is a hydrogen atom, a methyl group or a hydroxymethyl group;

R^1 is a substituted C_{1-12}alkyl group which group is substituted by at least one of the substituents A, defined below;

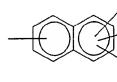
R^2 and R^3 are each selected from a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-5}alkoxy group, a carboxy group, a C_{2-7}alkoxycarbonyl group, a C_{1-5}alkyl group, a nitro group, a haloC_{1-4}alkyl group, or a substituted C_{1-12}alkyl group which group is substituted by at least one of substituents A, defined below;

X is an oxygen atom or a sulphur atom; and

Ar is a group of formula (C) or (D):



(C)



(D)

in which:

R^4 is a hydrogen atom, a halogen atom, a hydroxy group, a hydroxymethyl group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, an aliphatic carboxylic C_{1-6}acyloxy group, a nitro group, a cyano group, an aralkyloxy group in which the aralkyl part is as defined below, an aryloxy group in which the aryl part is as defined below, an aryl group as defined below, or a haloC_{1-4}alkyl.group;

R^5 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, or a nitro group;

R^6 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, or a C_{1-5}alkyl group;

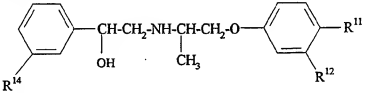
said aralkyl part is a C_{1-3}alkyl group which group is substituted by 1 or 2 aryl groups as defined below;

said aryl groups are carbocyclic C_{6-10}aryl groups which are unsubstituted or are substituted by at least one of substituents B, defined below;

said substituents A are selected from carboxy groups, C_{2-7}alkoxycarbonyl groups, aryloxycarbonyl groups in which the aryl part is as defined above, aralkyloxycarbonyl groups in which the aralkyl part is as defined above, C_{1-6} alkylcarbamoyl groups, dialkylcarbamoyl groups in which each alkyl part has from 1 to 4 carbon atoms, carbamoyl groups, hydroxycarbamoyl groups, hydroxy groups, carboxylic acyloxy groups having from 1 to 6 carbon atoms, and 2,4-dioxothiazolidin-5-yl groups; and

said substituents B are selected from halogen atoms, C_{1-4}alkyl groups, C_{1-3}alkoxy groups, nitro groups, haloC_{1-4}alkyl groups, and hydroxy groups; or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of an inflammatory gastrointestinal disorder.

14. The use as claimed in Claim 13 wherein the compound of formula (I), or physiologically acceptable salt or solvate thereof, as selected from compounds of formula (II).



(II)

and physiologically acceptable salts and solvates thereof,
wherein
one of R^{11} and R^{12} represents a hydrogen atom and the other of R^{11} and R^{12} represents the group $-CH_2CO_2H$; and
R^{14} represents a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group.

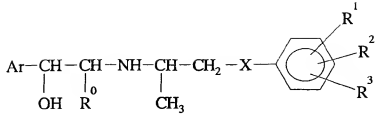
15. The use as claimed in Claim 4 wherein R^{11} is $-CH_2CO_2H$.

16. The use as claimed in any one of Claims 13 to 15 wherein the compound of formula (I) is (R,R)-[4-[2-[2-[(3-chlorophenyl)-2-hydroxy-ethylamino]propoxy] phenyl]acetic acid;

17. The use as claimed in any one of Claims 13 to 16 wherein the inflammatory gastrointestinal disorder is an inflammatory bowel disease selected from ulcerative colitis, ileitis, Crohn's disease and proctitis.

18. The use as claimed in any one of Claims 13 to 16 wherein the inflammatory gastrointestinal disorder is a condition of gastrointestinal ulcerations, said condition induced by non-steroidal anti-inflammatory drugs.

19. A pharmaceutical composition comprising a compound of formula (I)



(I)

wherein

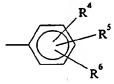
R^0 is a hydrogen atom, a methyl group or a hydroxymethyl group;

R^1 is a substituted C_{1-12}alkyl group which group is substituted by at least one of the substituents A, defined below;

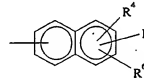
R^2 and R^3 are each selected from a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-5}alkoxy group, a carboxy group, a C_{2-7}alkoxycarbonyl group, a C_{1-5}alkyl group, a nitro group, a haloC_{1-4}alkyl group, or a substituted C_{1-12}alkyl group which group is substituted by at least one of substituents A, defined below;

X is an oxygen atom or a sulphur atom; and

Ar is a group of formula (C) or (D):



(C)



(D)

in which:

R^4 is a hydrogen atom, a halogen atom, a hydroxy group, a hydroxymethyl group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, an aliphatic carboxylic C_{1-6}acyloxy group, a nitro group, a cyano group, an aralkyloxy group in which the aralkyl part is as defined below, an aryloxy group in which the aryl part is as defined below, an aryl group as defined below, or a haloC_{1-4}alkyl group;

R^5 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, a C_{1-5}alkyl group, or a nitro group;

R^6 is a hydrogen atom, a halogen atom, a hydroxy group, a C_{1-5}alkoxy group, or a C_{1-5}alkyl group;

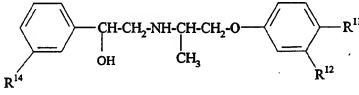
said aralkyl part is a C_{1-3}alkyl group which group is substituted by 1 or 2 aryl groups as defined below;

said aryl groups are carbocyclic C_{6-10}aryl groups which are unsubstituted or are substituted by at least one of substituents B, defined below;

said substituents A are selected from carboxy groups, C_{2-7}alkoxycarbonyl groups, aryloxycarbonyl groups in which the aryl part is as defined above, aralkyloxycarbonyl groups in which the aralkyl part is as defined above, C_{1-6} alkylcarbamoyl groups, dialkylcarbamoyl groups in which each alkyl part has from 1 to 4 carbon atoms, carbamoyl groups, hydroxycarbamoyl groups, hydroxy groups, carboxylic acyloxy groups having from 1 to 6 carbon atoms, and 2,4-dioxothiazolidin-5-yl groups; and

said substituents B are selected from halogen atoms, C_{1-4}alkyl groups, C_{1-3}alkoxy groups, nitro groups, haloC_{1-4}alkyl groups, and hydroxy groups; or a physiologically acceptable salt or solvate thereof, a non-steroidal anti-inflammatory drug and a physiologically acceptable carrier therefor.

20. A pharmaceutical composition as claimed in Claim 20 wherein the compound of formula (I), or physiologically acceptable salt or solvate thereof, is selected from compounds of formula (II):



(II)

and physiologically acceptable salts and solvates thereof,

wherein

one of R^{11} and R^{12} represents a hydrogen atom and the other of R^{11} and R^{12} represents the group $-CH_2CO_2H$; and

R^{14} represents a chlorine, fluorine or bromine atom or a methyl or trifluoromethyl group.

21. A pharmaceutical composition as claimed in Claim 20 wherein R^{11} is $-CH_2CO_2H$.

22. A pharmaceutical composition as claimed in any one of Claims 19 to 21 wherein the compound of formula (I) is (R,R)-[4-[2-[2-[(3-chlorophenyl)-2-hydroxy-ethylamino]propoxy] phenyl]acetic acid.

INTERNATIONAL SEARCH REPORT

Internation. pplication No
PCT/EP 94/02106

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/165 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP,A,0 543 662 (SANKYO COMPANY LIMITED) 26 May 1993 cited in the application see the whole document ---	1-22
A	J.MED.CHEM., vol.21, no.9, 1978 pages 922 - 930 W.J.DUNN III ET AL. 'Structure-Activity Study of beta-Adrenergic Agents Using the SIMCA Method of Pattern Recognition' see the whole document ---	1-22
Y,P	EP,A,0 556 880 (GLAXO GROUP LIMITED) 25 August 1993 see the whole document ---	1-22
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 November 1994	14. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Theuns, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 473 285 (IMPERIAL CHEMICAL INDUSTRIES PLC) 4 March 1992 see the whole document ---	1-22
Y	EP,A,0 516 349 (IMPERIAL CHEMICAL INDUSTRIES PLC) 2 December 1992 see the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

Internatio. application No.
PCT/EP 94/02106

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internation. ,pplication No
PCT/EP 94/02106

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CN-A- 1069023	17-02-93
		JP-A- 5148196	15-06-93